Perchlorate Initiatives

- Historical Perspective and Background
- Air Force and PSG Partnership
- TERA Peer Review Process and Objectives
- March and May Review Meetings
- Toxicology Studies - Status
- Data Evaluation and RfD Revision
- External Peer Review - Next Steps?

Historical Perspectives - Basis for the Provisional RfD

- Initial correspondence to EPA Region IX (Dec 92) from Superfund Health Risk Technical Support Center
  - NOAEL=0.14mg/kg-day (Stanbury & Wyngaarden)
  - Uncertainty Factor (UF) = 1,000
    - intrahuman variability (10)
    - less than chronic data (10)
    - database deficiencies (10)
- Drinking water criteria = 3.5 ppb based on 70kg/2 L water

Basis for theProvisional RfD (continued)

- Revision based on PSG submission to Superfund Health Risk Technical Support Center
  - NOAEL=0.14mg/kg-day (Stanbury & Wyngaarden)
  - Uncertainty Factor (UF) = 300
    - intrahuman variability (10)
    - less than chronic data (10)
    - database deficiencies decreased (3)
- Drinking water criteria = 18 ppb based on 70kg/2 L water

Air Force and PSG Involvement March 1997 - Peer Review Meeting

- ITER Peer Review
  - Parallels IRIS format
  - Representatives
    - Government (state and federal)
    - Industry
    - Health Canada
    - Environmental Group
- One of 3 Chemicals Reviewed

Peer Review Process

- Independent experts were selected from government, industry, academia, consultants, and environmental groups by *TERA* Board of Trustees

  Conflict of interest disclosed by reviewers and discussed by panel at review meeting in March 1997; decisions on managing made by panel consensus
- Review of perchlorate RfD lasted 3 hours with this format:
  - presentation by sponsor
  - discussion by panel of database, hazard identification, dose response, and other issues
  - opportunity for registered observers to comment
  - polling panel for consensus
  - identification of outstanding issues

ITER Perchlorate Objectives

- Evaluate data presented on perchlorate to establish a peer reviewed reference dose (RfD)
  - NOAEL=0.14mg/kg-day (Stanbury & Wyngaarden)
  - Uncertainty Factor (UF) = 1,000
    - intrahuman variability (10)
    - less than chronic data (10)
    - database deficiencies (10)

March Peer Review Participants

- Dr. Robert Benson, U.S. EPA, Region VIII
- Dr. John Christopher*, California EPA
- Dr. Gary Diamond, Syracuse Research Corporation
- Dr. Marvin Friedman, Cytec Industries, Inc.
- Ms. Annie Jarabek, U.S. EPA, National Center for Environmental Assessment
- Ms. Bette Meek, Health Canada
- Dr. Kenneth Poirier, Procter and Gamble Company
- Dr. Jon Reid, University of Cincinnati
- Ms. Ruthann Rudel, Silent Spring Institute
- Experts Available to Peer Review Panel
  - Dr.James Fagin, University of Cincinnati Department of Endocrinology
  - Dr. Charles Capen, Ohio State University Department of Veterinary Biosciences
  - Dr. Daniel Caldwell, principal investigator of the Caldwell et al. (1996) study

* Dr. Christopher was not polled for consensus

March Peer Review Outcomes

- Insufficient Data
- Recommended additional studies to be conducted
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Partnering Objectives for Perchlorate

- To get the best scientific information on the toxicology of perchlorate for use by the decision makers and most importantly to the public
- Target areas of uncertainty to fill in data gaps
- Partner with all stakeholders
- Continue working on possible cleanup technologies and evaluating analytical methods

May Panel Objectives

- Bring together the experts to determine what toxicology studies need to be conducted and secure the necessary funding and support
- Prioritize studies without regard to funding
  - Must do
  - Try to do
  - Interesting

May Perchlorate Study Protocol Review Meeting

- Dr. Joe Brown, California EPA, Office of Environmental Health Hazard Assessment
- Dr. Dan Caldwell, Toxicologist, Belle Meade, NJ
- Dr. Dorothy Canter, U.S. EPA, Office of Solid Waste and Emergency Response
- Dr. Charles Capen, Ohio State University, Department of Veterinary Biomedicine
- Dr. John Christopher, California EPA, Department of Toxic Substances Control
- Dr. Marvin Friedman, Cytec Industries, Inc.
- Mr. Greg Harvey, U.S. Air Force, Wright-Patterson Air Force Base
- Ms. Annie Jarabek, U.S. EPA, National Center for Environmental Assessment
- Dr. David Morry, California EPA, Office of Environmental Health Hazard Assessment
- Dr. Marilyn Underwood, California Department of Health Services
- Dr. David R. Mattie, AFRL, USAF

May Panel Outcomes

- Prioritized list of 8 Studies
- Agreement to continue as reviewers to develop and refine study protocols
- All final protocol information to be made available to the public through use of the world-wide-web on TERA's site
- Add reviewers and experts as needed
- Look for public educational opportunities

May 1997

Studies and Areas of Scientific Uncertainty In Reference Doses

STUDY	Description	H	A	S	D	L	Study's Usefulness
1. Neurobehavioral Developmental	tests nervous system of fetal, newborn and young animals	X			X		tests whether young animals are more sensitive than adults; may reduce H and may reduce D factor
2. 90-day, all other organs	tests many organs of young adult animals				X		Minimum database for RfD derivation; may reduce D factor
3. Receptor kinetics (in vitro studies; perchlorate discharge tests)	tests for mechanism of toxicity	X	X				shows if uncertainty factors for H and A can be changed from default values of 10
4. Segment II developmental	tests for birth defects				X		will reduce D factor
5. ADME - Absorption, Distribution, Metabolism and Elimination	compares how perchlorate is absorbed, metabolized, and excreted in animals and humans	X	X		X		Helps to evaluate if uncertainty factors for H and A can be changed from default values of 10; may affect value of D factor
6. Mutagenicity/ Genotoxicity	tests for mutations and toxic effects on DNA			X	X		may affect value of S and D factor
7. Reproductive	tests for reproductive performance in adults, and for toxicity in young animals				X		will reduce D factor
8. Immunotoxicity	tests for immunotoxicity in adults				X		may reduce value of D factor

Uncertainty factors for developing RfDs are as follows:
H = average human to sensitive human
S = short term to long term studies
D = data base deficiencies
A = animal to human
L = LOAEL to NOAEL

Protocol Review Team (as of 12 Jan 98)

- **Joe Brown, California EPA, Office of Environmental Health Hazard Assessment (OEHHA)**
- **Dan Caldwell, Toxicologist, Belle Meade, NJ**
- **Dorthy Canter, US EPA (OSWER)**
- **Charles Capen, Ohio State University**
- **John Christopher, California EPA, DTSC**
- **Eric Clegg, US EPA (NCEA)**
- **Kevin Crofton, US EPA National Health and Environmental Effects Research Laboratory (NHEERL)**
- **Vicki Dellarco, US EPA (OW)**
- **Marvin Friedman, Cytec Industries, Inc**
- **Greg Harvey, USAF, Wright Patterson AFB**
- **Annie Jarabeck, US EPA (NCEA)**
- **Kevin Mayer, US EPA (Region IX)**
- **David Morry, California EPA (OEHHA)**
- **MaryJane Selgrade, US EPA (NHEERL)**
- **Marilyn Underwood, California Department of Health Services**
- **Brenda Pohlmann, Nevada Division of Environmental Protection**

Studies, Cost and Time Frame

STUDY	Description	4Q97	1Q98	2Q98	3Q98	4Q98	Cost (thosands)	Sponsor
1. Neurobehavioral Developmental	tests nervous system of fetal, newborn and young animals	X	X	X			350	USAF
2. 90-day, all other organs	tests many organs of young adult animals	X	X	X			350	USAF
3. Receptor kinetics (in vitro studies, perchlorate discharge tests)	tests for mechanism of toxicity	X	X				in house literature review	USAF
4. Segment II developmental	tests for birth defects		X	X			101*	PSG
5. ADME - Absorption, Distribution, Metabolism and Elimination a. *Literature Review* b. Kinetics Proposals c. Throid Mechanistic Study (3 phases)	compares how perchlorate is *absorbed, metabolized, and* excreted in animals and humans	X	X	X X X	 X X	 X	*Internal* 200 (USAF) 150+ (RTP)	USAF/PSG NASA NASA
6. Mutagenicity/ Genotoxicity	tests for mutations and toxic effects on DNA		X	X			37	PSG
7. Reproductive	tests for reproductive performance in adults, and for toxicity in young animals		X	X	X	X	334*	PSG
8. Immunotoxicity	tests for immunotoxicity in adults			X	X	X	275	US Army

* Does not include the analysis of thyroid hormones. If needed, this work is estimated to cost between 55 and 85 thousand dollars.

Toxicity Study Review and RfD* Revision

- Review of existing and new toxicity data
- Hazard identification
- Dose-response evaluation
  - Evaluation of Critical effect
  - Designation of effect level - mathematical modeling or NOAEL / LOAEL procedure
  - Assignment of Uncertainty Factor(s)
  - Uncertainty Characterization - Confidence Statements
- Internal peer review
- External peer review
- IRIS process*

* Revision of the oral RfD has received a commitment. If an inhalation RfC and the unit risk estimates (oral and inhalation) can be evaluated without significant additional delay, then this may be considered. Advantage would be easier entry into IRIS process.

U.S. EPA Perchlorate Toxicity Assessment Team

◆ Harlal Choudhury	NCEA	general toxicology / risk assessment
◆ Eric Clegg	NCEA	reproductive toxicology
◆ Kevin Crofton	NHEERL	neurotoxicology
◆ Vicki Dellarco	OW	genetic toxicology
◆ Annie Jarabek	NCEA	general toxicology / risk assessment
◆ Gary Kimmel	NCEA	developmental toxicology
◆ MaryJane Selgrade	NHEERL	immunotoxicology